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Importance of Bone Markers and Radiological Status on Clinical Signs of Temporomandibular Joint Disorders

Oksana Ivask, Ülle Voog-Oras and Edvitar Leibur

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Abstract

This chapter describes the diagnostics of temporomandibular joint disorders (TMDs) with the main focus on the radiographic changes and the role of different bone markers as procollagen type I N-terminal propeptide (P1NP), C-telopeptide crosslaps of type I collagen (CTX-1) as well as vitamin D (25(OH)D) in the pathogenesis of TMDs. From our population-based study, 47% subjects had TMJ problems where pain is commonly accompanied by stiffness, sounds and functional limitations, resulting in a decreased quality of life, and thus exert a significant negative impact on activities of daily living (ADL). Assessment of individual pain level is important in the evaluation of TMD. Radiographic examination is commonly used for assessment of TMJ problems. Orthopantomograph (OPTG) is the most routine method for assessment of bone structural changes as erosions, flattening and osteophytes of the condyle and temporal part of TMJ. It is found that subjects with increased levels of P1NP, CTX-1 have less TMJ pain/discomfort. Increased levels of CTX-1 would probably cause an immediate increase of P1NP which is known as a sensitive marker of bone formation. TMJ radiographic changes seem to be related to the low level of 25(OH)D level.

Hence, the aim of this chapter is to critically review the evidence of possible association between TMJ pain and bone radiographic changes with main focus on the role of different bone markers and vitamin D.

Keywords: Activities of daily living, biochemical markers, OPTG, osteoporosis, pain measurement, temporomandibular joint disease, vitamin D

1. Introduction

Temporomandibular joint disorders (TMDs) present an important health problem. It has been estimated that approximately 20% to 30% of the adult population will experience temporomandibular joint (TMJ) dysfunction [1,2].

The most signs and symptoms include facial and jaw pain which can be initiated by jaw movements, TMJ sounds and functional disability. Radiological investigation often shows the displacement of the disc from its normal location, or osteoarthritic changes in the TMJ. Many researches focus on the role of biochemical mediators in development and progression of TMJ pain and dysfunction. There has been found association between bone markers (procollagen type I N-terminal propeptide (P1NP), C-telopeptide crosslaps of type I collagen (CTX-1) as well as vitamin D (25(OH)D) and TMD [3,4,5]. Several biochemical markers of bone turnover can be used to predict individual bone loss on risk for TMJ pathologies [6].

The globally increasing prevalence of TMD calls for a more detailed knowledge on the relationship between bone markers and vitamin D in the pathogenesis of TMJ disorders. The Northern Europe population has a high risk for D-hypovitaminosis [7]. There is still a lack of the knowledge of the specific impact of TMJ pain on daily activities in patients with clinical involvement of the TMJ. Hopefully, the new knowledge of the TMJ etiopathogenesis will help predict TMJ bone destruction. Additional vitamin D consumption might be suggested to avoid TMJ dysfunctions and thereby reduce pain level. A multidimensional understanding of the etiopathogenesis of TMJ pathologies detected at an earlier stage would help improve diagnostics and apply evidence-based treatment.

2. Temporomandibular joint disorders and pain

2.1. TMJ pain

Pain in the jaw musculature is the most commonly reported pain of nondental origin in the orofacial region [8]. The TMJ pain is common among all age groups [9]. Chronic craniofacial pain conditions with a prevalence of approximately 10–15% are increasing in the adult population [10,11,12]. The prevalence of TMJ pain across lifetime is still debated, but there seems to be a peak of the pain at approximately 45 years of age for women, although also elderly people may suffer from TMD pain [13]. Pain is always a subjective experience, and the impact of chronic pain is not just a sensory experience but also an emotional experience [14,15,16].

Chronic pain may be nociceptive, neuropathic, ischemic, visceral or exhibit a combination of different etiologies. Nociceptive pain may result from the stimulation of nociceptors at the nerve endings and is characteristically present in TMDs. Stress, somatic distress and depression may be potential etiological risk factors for TMDs-related pain. In chronic pain, psychological factors may become more obvious and prominent [17]. In a population-based study, 47% subjects had TMJ problems where pain is commonly accompanied by stiffness, sounds and functional limitations, which result in a decreased quality of life, and thus exert a significant negative impact on activities of daily living (ADL) [5]. The following everyday activities such as eating, talking, yawning and laughing were more disturbed [18,19,20]. It was found that the impact of TMJ pain/discomfort was the greatest on eating (ADL 9) in 68% of the men and 77% of the women and smallest on performing daily household chores (ADL 3) in 37% of the men and in 61% of the women (Table 1) [5].

	Median	IQR	% pos.	Median	IQR	% pos.
ADL questions		Male			Female	
ADL1	0	4	45	3	5	74
ADL2	0	3	37	2	4	68
ADL3	0	3	37	2	4	61
ADL4	1	5	50	4	6	68
ADL5	0	3	37	2	5	74
ADL6	0	3	45	3	5	67
ADL7	1	5	50	3	6	67
ADL8	2	5	53	3	5	74
ADL9	3	7	68	3	4	77
ADL11	0	3	50	3	6	68
ADL12	1	4	58	3	4	75

IQR = interquartile range, % pos: percentage of observations exceeding zero, ADL scale: 0–12, socialize with family and close friends? (ADL 1), perform daily work? (ADL 2), perform daily household chores (preparing meals, cleaning, taking care of small children)? (ADL 3), sit in a company or participate in other social activities (e.g. parties)? (ADL 4), exercise (walk, bicycle, jogging, etc.)? (ADL 5), perform hobbies (read, fish, knit, play an instrument)? (ADL 6), sleep at night? (ADL 7), concentrate (ADL 8), eat (chew, swallow)? (ADL 9), talking (laughing, singing)? (ADL 10), yawn, open mouth wide? (ADL 11), how much does the pain/discomfort affect your daily activities? (ADL 12) where 0 = activity without any pain/discomfort at all and 12 = activity impossible due to pain/ discomfort.

Table 1. The influence of temporomandibular joint pain/discomfort on activities of daily living

2.2. Temporomandibular joint Disorders (TMD)

Temporomandibular joint disorders refer to several clinical conditions that involve muscles of mastication and TMJ or both [21]. Also, TMD are associated with disc displacement [22]. The etiology of TMD is multifactorial, being related to factors such as stress, muscle hyperactivity, arthrogenous factors, parafunctions or the anatomy of the TMJ [23]. The knowledge of the pathogenesis on a molecular level of disorders of the TMJ has been improved by allowing a possibility to use these data for the evidence-based treatment [24–26].

Signs and symptoms of TMD may include pain, impaired jaw function, malocclusion, deviation or deflection, limited range of motion, joint noise and locking. Headache, tinnitus, visual changes and other neurologic complaints may also accompany TMD. It has been found that 28% of the adult population have signs of temporomandibular joint disorder, with higher prevalence in women at reproductive ages [11,27–29]. Women report more pain, TMJ pain of longer duration, higher clinical and experimental pain intensity and lower pain thresholds [30]. Together with arthralgia of the temporomandibular joints, it is collectively referred to as ‘temporomandibular disorder’ [8].

The TMJ involvement may occur in systemic rheumatic diseases (rheumatoid arthritis, psoriatic arthritis, etc.), secondary from the neighbouring regions (otitis, maxillary sinusitis,

tonsillitis), trauma (chronic), prevalence of dental arch defects, e.g. missing of molar teeth, malocclusion, endocrinological disturbances, odontogenic infections [31]. Many specific bacteria and several inflammatory mediators play an important role in the pathogenesis of TMJ diseases [32-34]. These inflammatory mediators drive catabolic pathways, inhibit matrix synthesis and promote cellular apoptosis. The bone loss at the TMJ condyle involves a common resorptive pathway: cytokine-activated osteoblasts promote activity of osteoclasts, which in turn result in the secretion of enzymes that are responsible for the breakdown of hydroxyapatite and collagen [35].

The most common form of TMJ arthritis is osteoarthritis (OA). It is one of the chronic diseases that involves TMJ [2]. The OA is classified as follows: (a) primary, which is idiopathic, i.e. factors are unknown; (b) secondary, where local and systemic factors are identified. It is mentioned that in secondary OA systemic causes are related to ethnicity, nutritional factors, genetics, hormonal status and bone metabolism, where as local causes include obesity, mechanical environment, overloading of articular cartilage and acute joint injury [36,37]. Most scientists regard osteoarthritis as an inflammatory process, being the most frequent TMJ disorder, characterized by proliferative changes in the synovia and primary degeneration of the cartilage and surrounding tissues with destruction of the bone structures and causing TMJ pain [24,38]. Nowadays, it is increasingly recognized that OA is a disease of the whole joint that affects all articular structures, including articular cartilage, subchondral bone, synovium, tendons, ligaments and menisci. The role of bone and articular soft tissues in the pathophysiology of OA has been widely overlooked [39].

3. Diagnostics of temporomandibular joint disorders

3.1. Activities of Daily Living (ADL) and the Visual Analogue Scale (VAS)

The impact of pain on the health status and quality of life in patients with chronic inflammatory joint diseases has been recognized, but there is a lack of knowledge about the specific impact of TMJ pain on daily activities in patients with clinical involvement of the TMJ [18]. Assessment of the individual level of daily activities is important in the evaluation of TMD. There are several scales for assessing patients' TMJ functions and for describing the particulars of their disability and the fact how their current status reflects in their day-to-day activities.

The term 'activities of daily living' (ADL) has been used to denote activities undertaken as part of a person's daily functions [40]. The ADL scale by Katz et al. [41] was primarily designed to measure the ability to carry out every day activities necessary for daily living. It has been validated and modified for specific use in patients with TMJ disorders [18,42-44]. Use of an ADL questionnaire is a very convenient method for pain assessment. This questionnaire is very simple and easy to handle and it can be recommended for future clinical trials in patients with TMJ disorders [45,46]. Only a few systematic reviews have addressed to daily activities or quality of life in relation to management of TMJ disorders. It is concluded that the use of specific questionnaires is justified for assessment of the character of TMJ pain [5].

The visual analogue scale (VAS) is a single-item scale to measure pain intensity [47]. The VAS is a continuous scale comprised of a horizontal or vertical line, usually 10 cm (100 mm) in length, anchored by two verbal descriptors, one for each symptom extreme. For pain intensity, the scale is most commonly anchored by 'no pain' (score of 0) and 'pain as bad as it could be' or 'worst imaginable pain' (score of 100 [100-mm scale; 48,49]. The VAS was initially used in psychology by Freud in the early 1900s and was elaborated in rheumatology through a series of investigations by Huskisson et al. in the late 1970s [50]. The scale has a high degree of sensitivity and validity because slight changes in pain intensity can be detected; however, it can also be confusing in a way for both very young and elderly patients [51,52]. The VAS scale has been used in several TMJ studies [53–56].

3.2. Radiographic imaging

Radiographic examination is commonly used for assessment of TMJ problems. Radiographic changes of the TMJ can be evaluated by orthopantomography, computed tomography and magnet resonance imaging [57,58] among other techniques, as well as by ultrasonography [59].

3.2.1. Orthopantomography (OPTG)

Orthopantomography (OPTG) is most commonly used for assessment of bone changes in the TMJ. By evaluating OPTGs, the following radiographic signs of bone structural changes can be detected, such as presence of erosions, flattening and osteophytes of the TMJ condyle as well as of temporal bone [60,61]. OPTGs give the possibility to describe structural changes in bone in different regions as alveolar cortical thickness of the mandible, lamina dura width, alveolar bone height, mandibular bone mineral density (BMD) and status of teeth [62–66]. The studies have shown that mandibular cortical shape on OPTGs may be an indicator of bone turnover and spine BMD [67–70].

The most visible radiographic sign in the TMJ by OPTG is erosion (Figure 1).



Figure 1. Orthopantomograph. Subchondral bony erosions of the right mandibular condyles are visible. Narrowing of both temporomandibular joint spaces and an irregularity of joint surfaces is observed.

The mandibular cortical erosion has been significantly associated with increased N-telopeptide cross-links of type I collagen and alkaline phosphatase levels [71]. Recent investigations have shown that radiographic examination including OPTG may be an effective tool as primary changes appear in alveolar bone for the early diagnosis of osteoporosis [4,72–75]. OPTGs could be useful as a simple screening method to estimate bone structure changes in the TMJ as well as to provide valuable information about the quality of the jaw bone such as joint space narrowing, osteophytes, subchondral sclerosis and subchondral cysts [76].

The total sum of radiographic changes in the TMJ is observed in 57% of the participants. Erosions occurred in 80%, flattening occurred in 37% and osteophytes occurred in 5% of the participants (Figure 2) [77].

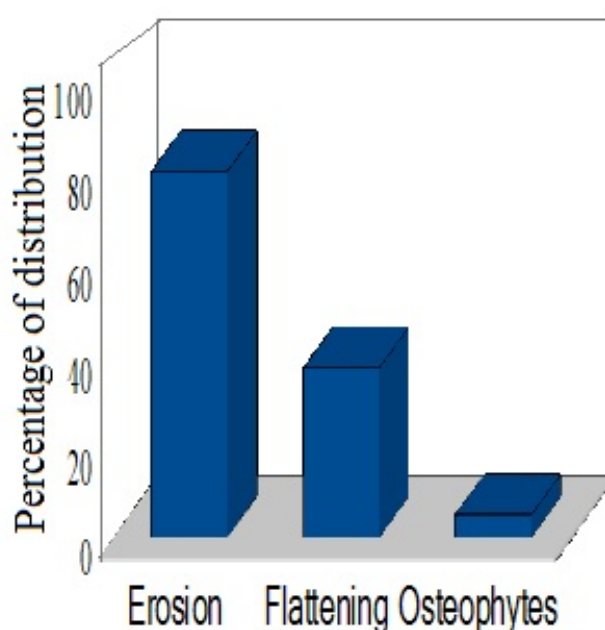


Figure 2. Distribution of radiographic changes.

3.2.2. Computed Tomography (CT)

The first report of TMJ computed tomography (CT) was published by Suarez et al. in 1980 [78] and this method is superior to plain transcranial or transmaxillary imaging for detecting bone changes. CT allows detailed three-dimensional examination of the TMJ and it is capable to detect even small bone changes not demonstrable by conventional tomographic procedures [2,79]. According to Rohlin and Petersson [80], the changes can be investigated by CT as follows: erosion – a local area with decreased density of the cortical joint surface including or not including adjacent subcortical bone, sclerosis – a local area with increased density of the cortical bony joint surface that may extend into the subcortical bone, subchondral pseudocyst (a well-defined local area of bone rarefaction underneath an intact cortical outlining of the joint surface; Figure 3) and flattening (a flat bony contour deviating from the convex form osteophyte – a marginal bony outgrowth; Figure 4).

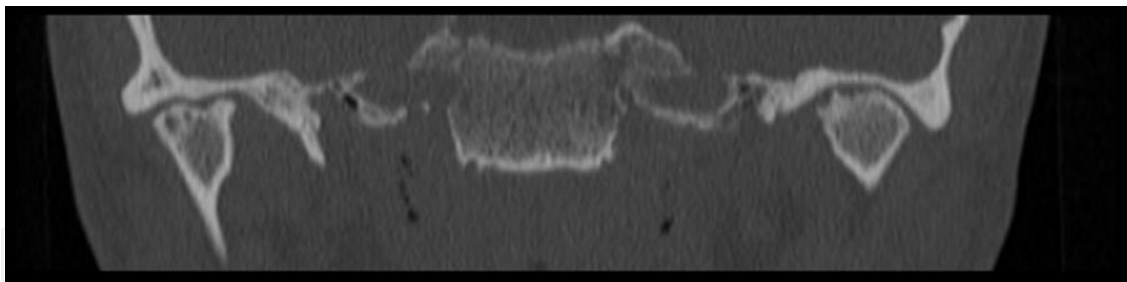


Figure 3. Osteoarthritis of TMJ. Bilateral signs of erosions on the surfaces of the condyles in a coronal view of the CT. Subchondral cyst in the right condyle. The joint spaces are asymmetric.

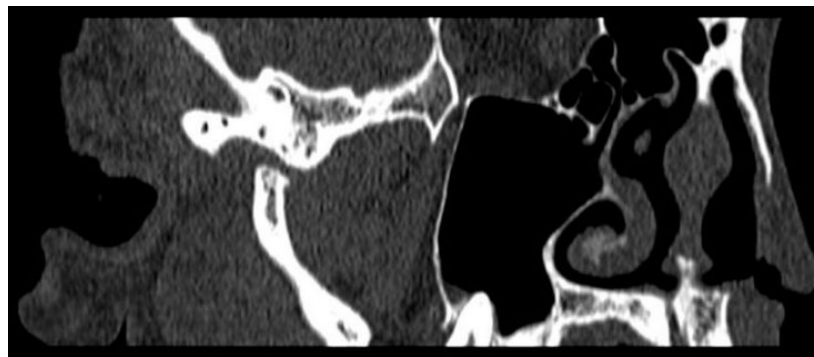


Figure 4. Sagittal view of the CT, right TMJ in an open mouth position. Sign of flattening of the mandibular condyle.

The CT allows to diagnose TMJ fractures, ankylosis, dislocation, neoplasms and growth abnormalities such as condylar hyperplasia [81]. The first choice for TMJ pathology diagnostics is OPTG; the CT imaging must improve treatment planning and prognosis.

4. The role of bone markers, vitamin D and osteoporosis in the pathogenesis of TMD

4.1. C-Telopeptidcrosslaps of type I collagen (CTX-1) and procollagen type I N-terminal Propeptide (P1NP)

Although several markers have been described to measure bone metabolism, it has been difficult to differ between the different mechanisms of bone resorption. These assays measure, in serum or in urine, enzymes or matrix proteins synthesized or degraded by bone cells [6]. It is stated that the most sensitive markers of bone resorption are C-telopeptidcrosslaps of type I collagen (CTX-1) and C-terminal telopeptide of type I collagen (1CTP), which are released from bone by different enzymatic pathways. The key osteoclastic enzyme for systemic bone resorption is generated by cathepsin K. The 1CTP is generated by matrix-metalloproteinases which plays an important role in collagen degradation associated with systemic inflammatory disease [82]. Procollagen type I N-terminal propeptide (P1NP) is a sensitive marker of bone

formation. P1NP is synthesized by osteoblasts from type I procollagen precursor proteins. These precursors have large extension domains at both ends. While type I collagen is being synthesized, type I aminoterminal and carboxyterminal propeptides, PINP and PICP, respectively, are enzymatically removed and released into the circulation [83]. As bone is the major structure synthesizing type I collagen, PINP and PICP reflect bone formation [84]. Bone markers provide information beyond that of a single bone density measurement and on the cellular process leading to bone loss [85]. However, some of the few studies have not reported relationship between biomarkers and BMD [86]. Serum bone biomarkers are associated not only with systemic BMD loss but also with alveolar bone loss [87]. Biomarkers have the potential to provide an early warning of the initiation of breakdown of the articular matrix, which in future could lead to earlier treatment to prevent joint destruction that leads to disability [88].

The markers of joint tissue metabolism have opened new possibilities for earlier diagnosis of radiographic changes in joints and of OA [89,90]. It is found [77] that subjects with increased levels of P1NP, CTX-1 have less TMJ pain/discomfort. Increased levels of CTX-1 would probably cause an immediate increase of P1NP, which is known as a sensitive marker of bone formation. Subjects with a lower BMD had significantly less occluding pairs of teeth (Figure 5).

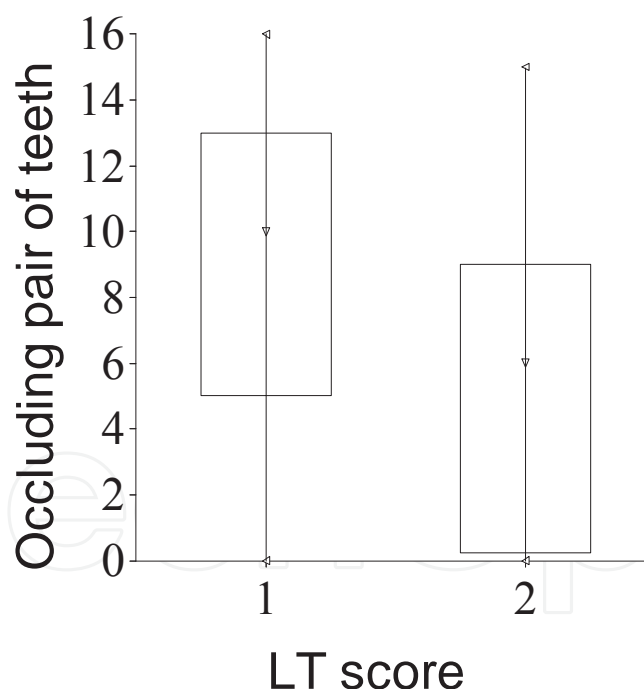


Figure 5. Relationship between occluding pair of teeth and LT score. Box plot showing the relationship between occluding pair of teeth and LT score. Box number 1 – subjects with normal mineral density. Box number 2 – subjects with lower LT score.

There are not enough data about the bone characteristics of patients with TMJ disorders. There still remains the question whether osteopenia in the TMJ area of the mandible is a local

manifestation of osteoporosis having similar aetiology and risk factors, or it is an independent process depending primarily on factors that cause bone structural changes in the TMJ [75]. All these points to the need for additional studies which would evaluate the influence of potential contributing factors to further define the relationship between bone markers and TMJ disorders in population.

4.2. Vitamin D (25(OH)D)

Vitamin D (25(OH)D) plays an important role in calcium and bone metabolism inhibiting cytokine production and cell proliferation in various tissues [91]. Low levels of vitamin D lead to compensatory elevation of parathyroid hormone, which can cause lowering of BMD and eventually osteoporosis [92,93]. Vitamin D is related to musculoskeletal functioning and has been associated with a lower incidence of several cancers and autoimmune diseases. Studies have also shown that vitamin D has a role in neuromuscular function [94-96].

A majority of studies examined the association between serum 25(OH)D concentration and physical performance in community-dwelling older adults [93,95,97-99]. In particular, elderly people have a higher risk of vitamin D insufficiency, but it affects all age groups [100,101]. Low levels of 25(OH)D in young people can be partly explained by inadequate dietary sources and low activity in the daytime. It is estimated that vitamin D inadequacy is present in 36% of healthy young adults and in 57% of general medicine inpatients in the United States [102,103]. Vitamin D insufficiency seems a common health problem for people who live in countries at high latitudes where sunshine hours are short in the winter. Also Vitamin D levels are affected by modifiable and non-modifiable factors such as diet, time outdoors, skin pigmentation, sunbathing habits and medications [104,105,106]. Limited clinical research has focused on the specific effects of vitamin D deficiency on jaw pain. It is reported that vitamin D deficiency can cause predisposition to TMJ disorders [5,77,107,108].

A number of studies have addressed the relationship between sex hormones and TMDs and between low levels of vitamin D and pain all over the body but have not described the relationship between vitamin D and TMDs.

It was found [5] that lowering of 25(OH)D correlated negatively with activities of daily living such as social life with family (ADL 1), other social activities (ADL 4), exercising (ADL 5), performing hobbies (ADL 6), concentrating (ADL 8), eating (ADL 9), how much the pain/discomfort affects daily activities (ADL 12; Fig. 6). The women had lower 25(OH)D level compared to the men.

4.3. Osteoporosis

Osteoporosis is one of the most common human bone diseases affecting millions of people, including over one-third of females above the age of 65 years and generally characterized by low bone mass, with increase in bone fragility and susceptibility to fracture. According to the World Health Organization, osteoporosis is considered to be present when BMD is 2.5 standard deviations (SD) below the young normal. Osteopenia is defined as bone density levels between 1 SD and 2.5 SD below normal BMD. Osteopenia is a reduction in bone mass due to imbalance

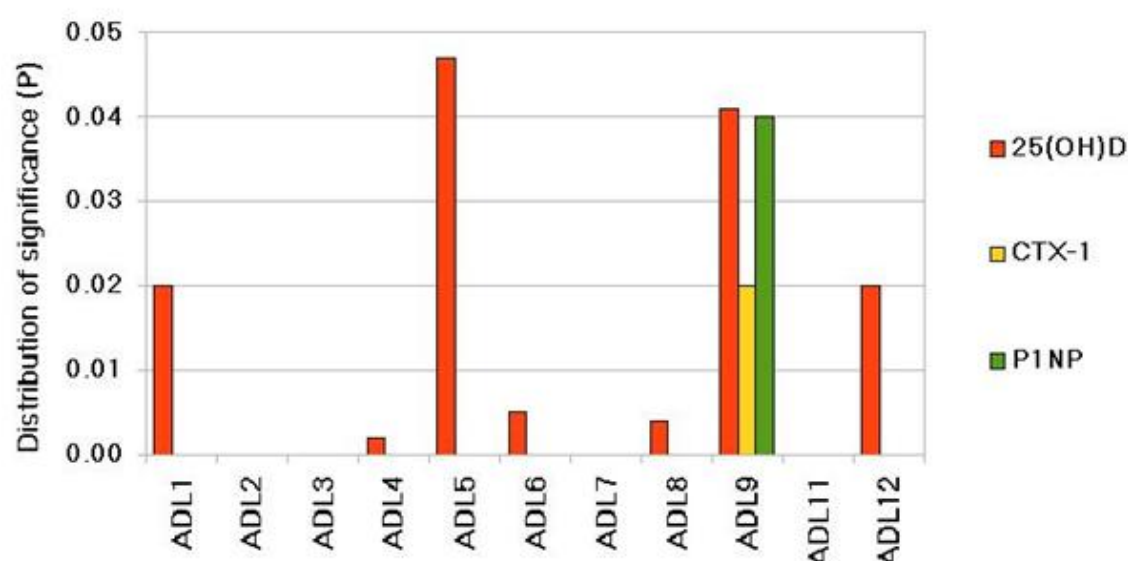


Figure 6. Distribution of significance between ADL data and bone characteristics. Relationship between bone characteristics and activities of daily living.

between bone resorption and formation, favouring resorption, resulting in demineralization and leading to osteoporosis [109]. The risk factors for osteoporosis are: sex, age, low body mass, early menopause, race, heredity, physical inactivity, lack of calcium intake, smoking and alcohol consumption [66].

The association between osteoporosis and oral bone disease was found already in 1960 [110]. Osteoporosis can affect all craniofacial and oral structures [76]. Osteoporosis is reported to cause bone loss in the alveolar processes of the maxilla and the mandible, which provides bony framework for tooth anchorage [111]. Some researchers have investigated whether dental radiographs could play a role in the detection of individuals with osteoporosis [112]. Bone mass in the jaw might be related to that of other skeletal sites in which osteoporosis was a significant problem [113,114]. The association between systemic osteoporosis and oral health remains controversial [115] while studies in this area are limited. Therefore, the relationship between systemic osteoporosis and oral health is still a complex problem of great interest for a large number of researchers and clinicians. Some epidemiological studies found that non-osteoporotic women's mandibular bone mass was not affected by age but was significantly associated with skeletal bone mass at the spine and wrist. The trabecular pattern was a highly significant predictor of future skeletal fracture risk [63,116]. Biochemical markers of bone turnover can be used to predict individual bone loss and therefore, they may help to alert patients to the risk of pathologies in the TMJ [4]. Thus, studies which evaluate the above mentioned contributing factors to define relationship between TMJ pain and several bone characteristics and ADL in population are justified.

The radiographic changes in the TMJ seem to be related to BMD. The patients with severe erosion of the cortex had significantly lower BMD values. In a population-based study was

found out of 95 participants, 42% had abnormally low values of LT score. Among them osteoporosis was observed in 10.4% and osteopenia in 31.6% [77].

5. Conclusion

It is demonstrated that pain/discomfort originating from the TMJ is influenced by the biochemical markers of bone turnover. TMJ radiographic changes and teeth loss seem to be related to the low levels of BMD and 25(OH)D. The finding leads to the possible role of 25(OH)D in lowering of BMD in the TMJ and eventually osteoporosis. These findings indicate that presence of lowering BMD seems to be as one of the predictors for TMJ bone destruction.

Associations between TMJ pain/discomfort with vitamin D with the activities of daily living is evident. Subjects with lower 25(OH)D values experienced difficulties in performing physical exercises, engaging hobbies, they have problems with eating, participating in static social gatherings or other social activities. The social life of these persons is disrupted to a considerable degree. The median value of TMJ pain in the male as well as in the female group was relatively high considering that the study sample consisted of voluntary participants. Comparing the different sexes, we found highly significant correlations between female gender in following activities of daily living: social life, performing daily work, performing daily household chores, exercising, performing hobbies and yawning and opening the mouth wide. The same correlations in male were less significant.

Low 25(OH)D level can predict TMJ bone destruction and additional vitamin D consumption might be suggested to avoid TMJ dysfunction.

It is found that subjects with increased levels of P1NP, CTX-1 have less TMJ pain/discomfort. Increased levels of CTX-1 would probably cause an immediate increase of P1NP, which is known as a sensitive marker of bone formation.

Correlation between these two markers is probably due to equal shift / balance in a normal bone metabolism, where osteoblasts are acting simultaneously with osteoclasts.

The tight interaction and coordination between different aspects of TMD can be as a puzzle for health professionals. Based on obtained knowledge, the accuracy of diagnosis, quality of treatment as well as care for TMD can improve in the nearest future.

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